ESMO Open Cancer Horizons

ESMO Management and treatment adapted recommendations in the COVID-19 era: Lung cancer

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To cite: Passaro A, Addeo A, Von Garnier C, *et al*. ESMO Management and treatment adapted recommendations in the COVID-19 era: Lung cancer. *ESMO Open* 2020;**5**:e000820. doi:10.1136/esmoopen-2020-000820

Received 5 May 2020
Revised 20 May 2020
Accepted 20 May 2020

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ABSTRACT

The COVID-19 pandemic, characterised by a fast and global spread during the first months of 2020, has prompted the development of a structured set of recommendations for cancer care management, to maintain the highest possible standards. Within this framework, it is crucial to ensure no disruption to essential oncological services and guarantee the optimal care.

This is a structured proposal for the management of lung cancer, comprising three levels of priorities, namely: tier 1 (high priority), tier 2 (medium priority) and tier 3 (low priority)—defined according to the criteria of the Cancer Care Ontario, Huntsman Cancer Institute and Magnitude of Clinical Benefit Scale.

The manuscript emphasises the impact of the COVID-19 pandemic on lung cancer care and reconsiders all steps from diagnosis, staging and treatment.

These recommendations should, therefore, serve as guidance for prioritising the different aspects of cancer care to mitigate the possible negative impact of the COVID-19 pandemic on the management of our patients. As the situation is rapidly evolving, practical actions are required to guarantee the best patients' treatment while protecting and respecting their rights, safety and well-being. In this environment, cancer practitioners have great responsibilities: provide timely, appropriate, compassionate and justified cancer care, while protecting themselves and their patients from being infected with COVID-19. In case of shortages, resources must be distributed fairly. Consequently, the following recommendations can be applied with significant nuances, depending on the time and location for their use, considering variable constraints imposed to the health systems. An exceptional flexibility is required from cancer caregivers.

INTRODUCTION

The coronavirus disease 2019 (COVID-19), characterised by a respiratory tract infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, to date has caused more than one million confirmed cases worldwide.[1] This pandemic has forced all the healthcare stakeholders to urgently reorganise the management of patients with COVID-19, prioritising per value resources and therapeutic strategies.[2 3]

Since the beginning of the outbreak of COVID-19, the oncology community has been under pressure to protect cancer patients and ensure their treatment.[4 5] This complex task required brings with it an emotional struggle as we balance the desire to cure or treat our patients, with the fear of losing them from infection.[6]

Several worldwide leading professional organisations, including the European Society of Medical Oncology (ESMO), have worked to implement and share knowledge about the importance of preventative/measures to maximise their support to our patients.[4 7]

Deciding whether to offer, postpone or even cancer or not treatments to patients, has become a crucial recurrent dilemma for lung cancer oncologists.[4 8] Different cancer treatments require careful specific, individual assessment and consideration: for instance, chemotherapy may cause transient immune suppression, immunotherapy or tyrosine kinase inhibitors may trigger inflammatory lung changes, mimicking and worsening pulmonary symptoms.[9] These inflammatory lung damage scenarios that are routinely faced in the contest of lung cancer care could potentially lead to a poorer outcome in case of concomitant COVID-19 disease. However, oncologists should weigh the risk of death for patients with lung cancer due to COVID-19, with the negative impact on their prognosis due to disruption of their cancer care.[9 10] Oncologists should not ignore the risk of observing a bimodal peak of cancer patients dying: the imminent spike of those falling victim to COVID-19 and the latent toll on those experiencing an excess of cancer-related mortality, whose treatments were de-intensified, delayed or cancelled.

Considering that the duration of this pandemic is difficult to foresee, patient decisions have to be made by multidisciplinary teams. A multifactorial risk/benefit

evaluation, including the magnitude of the epidemic in the country, the local healthcare structure resources and the infection risk to the individual, must be carried out.[11]

In the present work, we report the ESMO recommendations for diagnosis, treatment and follow-up for patients affected by lung cancer during the COVID-19 pandemic. These recommendations should be used as guidance to prioritise the various aspects of cancer care and to mitigate the potential harm due to COVID-19 epidemic on patients with lung cancer.

METHODOLOGY FOR THE SELECTION OF PRIORITY INTERVENTIONS

The present manuscript reports the consensus of an international panel of thoracic malignancies experts in the management of lung cancer. It is proposed to guide healthcare professionals treating lung cancer patients during the COVID-19 pandemic. The expert consensus-based recommendations are not intended to replace the current guidelines but slightly adapt them to the evolving circumstances and constraints imposed by the COVID-19 pandemic, using a value-based framework to set priorities. The experts have formulated all the adaptations and prioritisations via teleconferences and email discussions.

With the aim to provide a framework for the response of the medical community to COVID-19, ESMO has established guide for clinicians, defining three levels of priorities regarding therapeutic interventions, namely: tier 1 (high priority), tier 2 (intermediate priority) and tier 3 (low priority)—informed by the Ontario Health Cancer Care Ontario framework of resource-prioritisation and by the ESMO Magnitude of Clinical Benefit Scale (MCBS), a public health tool intended to support the uptake of medical interventions in oncology.[12 13]

Overall, the prioritisation has been developed to incorporate both the information on the value-based prioritisation and clinical cogency of the responses.

- **Tier 1 (high priority)**: patient's condition is immediately life-threatening, clinically unstable and/or the magnitude of benefit qualifies the intervention as high priority (eg, significant overall survival gain and/or substantial improvement of the quality of life (QoL));
- **Tier 2 (medium priority)**: patient's situation is non-critical but delay beyond 6 to 8 weeks could potentially impact the overall outcome and/or the magnitude of benefit qualifies for intermediate priority;
- **Tier 3 (low priority)**: patient's condition is stable enough allowing services to be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude of benefit (eg, no survival gain with no change or reduced QoL).

The clinical guidance defined by ESMO must be interpreted and used in the broader context of local and international health system strategies and aligned to the Global Norms of WHO, the lead public health agencies and health technical governmental boards. Interventions to ensure the safest conditions for the health workforce, the proper provision of personal protective equipment, the testing strategy for healthcare personnel, patients and communities are essential and developed in parallel, conditioned by the local situation over time. Of note, population-based strategies and policies need to consider the most vulnerable communities explicitly for COVID-19 infection and complications—cancer patients being first among them.[13 14] Recently, the TERAVOLT registry revealed that patients with thoracic malignancies are less likely to be admitted to the intensive care unit and are at increased risk of prolonged hospitalisation and mortality, rising to 33% in this series, from COVID-19 infection. Univariate analyses revealed that the presence of chronic obstructive pulmonary disease was associated with a risk of hospitalisation and death. A multivariate analysis is that no patient treatments or cancer-related factors were associated with a higher risk of death.[15]

PRIORITIES FOR LUNG CANCER PATIENTS

Outpatients visit priorities

The COVID-19 pandemic has been placing unprecedented pressure on health systems worldwide. To respect social distancing and to apply the overall public health measures for the mitigation of SARS-CoV-2 spread outpatient cancer services should be reinforced and reorganised. This must occur balancing; first, the risks for cancer patient to contract COVID-19 during investigations and treatments and, second, the care providers' capacity.

In the outpatient setting, prioritisation is guided by the magnitude of benefit. Clinical situation and quality of care should remain unchanged for the prioritised interventions.

For example, all treatment plans for patients with cancer must be discussed in a multidisciplinary setting as it has significant prognostic implications. Thus, while the format may change (eg, videoconferencing), the principle of multidisciplinary shared care is non-negotiable.[16]

A quick triage for possible symptoms of COVID-19 composed of a rapid questionnaire and temperature check should be put in place before entering any hospital premises.

To minimise the risk of exposure, outpatient visits should be reorganised: established patients with symptoms or patients with high suspicion of new lung cancer must be handled within standard pathways, ensuring protective measures are in place (eg, hand hygiene, physical distancing recommendations and use of personal protective equipment requested).[17]

Although hospital admission should be minimised, all the new cases with suspicion of clinical stage III or metastatic, both for non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC), or the appearance of disease-related symptoms (eg, dyspnoea, cough, chest pain, haemoptysis and so on) should keep the standard work-up as per standard guidelines, without undue delay (high priority) (table 1).

Table 1 Outpatient visit priorities

High priority	Medium priority	Low priority
New diagnosis or suspicion of invasive lung cancer with either: ► Disease-related symptoms (dyspnoea, pain, hemoptysis and so on) ► Suspicion of clinical stage III or metastatic NSCLC or SCLC	New diagnosis or suspicion of localised lung cancer of clinical stage I	Patients visits for psychological support (convert to telemedicine)
		Survivorship visits
	Follow-up for patients at high risk of relapse	Follow-up for patients at low/intermediate risk of relapse
Visits for treatment administration	Established patients with new problems or symptoms from treatment - convert as many visits as possible to telemedicine visits	Postoperative patients with no complications - convert as many visits as possible to telemedicine visits

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

All non-priority outpatient appointments may be converted to the telemedicine platform, evaluating the priority on a clinical need basis. Telemedicine suits best the non-urgent situations for established patients without new complaints as well as patients on long-term follow-up with low/intermediate risk of relapse. In asymptomatic patients on follow-up, radiological investigation can be delayed unless new symptoms occur (medium priority).

For some of the patients on active treatment, whenever possible, the consultations should be shifted to telemedicine and blood tests performed at home. Overall, in the context of oncology care, telemedicine might represent a valuable tool to implement, but it should not entirely replace standard practice.

The patient-centred care model requires addressing of all patient's needs and as such, psychosocial supports must be assured and converted to telemedicine or other web-based platforms if possible.

IMAGING

The role of imaging in lung cancer remains crucial for diagnosis and disease management. As recommended by the Centers for Disease Control and Prevention (CDC)[17] guidance and endorsed by the American College of Radiologist (RCR),[18] prioritising and safeguarding the healthcare resources is essential. Hence outpatient appointments and or imaging for non-critical patients, including a non-urgent diagnostic or image-guided procedure, should be postponed and rescheduled (low priority) (table 2).

Radiologists should closely work with their referring thoracic oncologists to review and reschedule such exams, based on patient's priorities, prognosis and symptoms (low priority).

Similarly, considering the risk-benefit ratio lung cancer screening protocol with low-dose CT scan should be temporarily withheld during the pandemic peak or the appointments at least postponed by a few weeks or months depending on the local situation.

Furthermore, as reported by the National Health Service (NHS) of England guidelines for the management of non-COVID-19 patients, alternative methods to monitor and review patients receiving systemic therapies should be explored. Nevertheless, slots for follow-up imaging within the first 6 months of lung cancer treatment or in case of possible progression disease at any point in time should remain unchanged (high priority).

It is highly recommended that all patients suspicious for lung malignancy could have priority access to diagnostic imaging (eg, CT scan, positron emission tomography scan) (high priority). Whenever this was not feasible in a local hospital, a transfer to a cancer hub should be considered.

LUNG CANCER SURGERY

During the COVID-19 pandemic, the capacity of thoracic surgery has been significantly reduced and access to the intensive care unit after elective surgery might have been restricted. Due to these restrictions, setting up a priority-framework for lung cancer surgery is essential.

The multidisciplinary team plays an essential role to prioritise different lung cancer surgical procedures while preserving the highest possible standards. Once again, risk/benefit ratio, including not only patients and disease aspects[19] but also alternative treatment modalities such as (chemo)radiation therapy for high volume disease or stereotactic ablative radiotherapy T1-T2N0 tumours, should be carefully explored (table 3).[20 21]

During the COVID-19 outbreak, keeping at bay the perioperative morbidity and mortality due to cancer or to SARS-CoV-2 infection should be a common goal. However, lung cancer is usually characterised by fast-growing behaviour; therefore, a rapid surgical assessment must be prioritised and carried out in particular if a delay could

Table 2 Imaging priorities for lung disease

High priority	Medium priority	Low priority
► Patients with significant respiratory symptoms and/or other clinically relevant chest, cancer-related or treatment-related symptoms. In patients with new respiratory symptoms such as dyspnoea, cough with or without fever, a CT scan is recommended	Follow-up imaging for high/intermediate risk of relapse in a year after completion of radical treatment	Follow-up imaging for high/intermediate risk of relapse more than one year after completion of radical treatment.
Standard staging work-up for suspected invasive cancer of unknown stage or stage II/III/IV	Standard staging work-up for early lung cancer (stage I)	Follow-up imaging after radical treatment in low-risk of relapse scenario.
Biopsies for suspicious nodules or mass for suspected invasive cancer of stage or stage III/IV	Biopsies for suspicious nodules or mass for suspected invasive cancer of unknown stage or stage I/II	
	Established patients with new problems or symptoms from treatment	
Evaluation of active treatment response in the first 6 months of treatment or if suspicion of progression at any time point	Evaluation of active treatment response beyond 6 months of treatment if stable/ controlled situation	
	Follow-up of nodules of incidental finding with either: ► Solid nodule 50 to 500 mm^3 ► Pleural-based solid nodule 5 to 10 mm ► Partially solid nodule with a non-solid component of ≥8 mm ► Known VDT 400 to 600 days	Follow-up of nodules of incidental finding with either: ► Solid nodule <50 mm^3 ► Pleural-based solid nodule <5 mm ► Partially solid nodule with a non-solid component of <8 mm ► Non-solid nodule <8 mm ► Benign morphology ► Known VDT>600 days
Pre-planned imaging evaluation per clinical trial protocol		Lung cancer screening can be deferred until the COVID-19 pandemic resolves - it is reasonable for patients in the general population to defer screening low-dose CT, a deferral that is not likely to have an impact on overall survival.

VDT, volume doubling time.

compromise the surgical outcome (high priority).[22] High priority must also be given to specific palliative surgical approaches as thoracentesis or stent insertion, in case of significant symptoms and in order to improve QoL and patients' prognosis.[23–25]

Surgical indications must be individualised, and all decisions should be shared with the patients and their caregivers: assessing preference and managing expectations while informing on the pros and cons of any plan in the context of the COVID-19 crisis remains crucial.[26]

EARLY STAGE NON-SMALL CELL LUNG CANCER

Improving outcomes in the curative setting of early stage remains a major therapeutic challenge in lung cancer management.

According to the ESMO-MCBS,[13] pharmacological interventions in the curative setting are scored A, on a scale from A to C, from high to low priority, respectively. Therefore, the selection and prioritisation of the medical treatments at these stages require prudence and long-term vision as overall survival remains the most relevant endpoint.

Adjuvant platinum-based doublet chemotherapy, in resected stage I to III of NSCLC, showed an absolute benefit in survival at 5 years of about 5% to 6%.[22] Since systemic treatments do not increase early mortality rates after surgery, tolerability and treatment adherence are critical factors for the optimum timing of chemotherapy in the COVID-19 era. Considering the risk of SARS-CoV-2 infection related to peri-surgical and post-surgical time and different chemotherapy aspects (eg, immunosuppressive state), the role of adjuvant chemotherapy at the present time should be reconsidered, based on a priority scale that includes mainly the relative survival benefit and functional comorbidities (table 4).

Table 3 Surgical oncology priorities for lung disease

High priority	Medium priority	Low priority
Drainage =/- pleurodesis of pleural effusion, pericardial effusion, tamponade risk		
Evacuation of empyema-abscess		
T2N0 tumours naïve from treatment or after induction chemotherapy	Discordant biopsies likely to be malignant	Discordant biopsies likely to be benign
Resectable T3/T4 tumours naïve from treatment or after induction chemotherapy		
Resectable N1/N2 disease naïve from treatment or after induction chemotherapy		Operable pure GGO nodule (T1a)
Operable NSCLC with T1AN0 (alternative if no surgical capacity available is stereotactic radiotherapy; surgery is preferred)		
Diagnostic procedure as mediastinoscopy / thoracoscopy / pleural biopsy / endoscopy / transthoracic investigations for diagnostic/ staging workup	Diagnostic work-up and/or resection of nodules of incidental finding with either: ► Solid nodule >500 mm^3 ► Pleural-based solid nodule >10 mm ► Solid component >500 mm^3 in partially solid nodule ► Known VDT <400 days ► New solid component in pre-existing non-solid nodule (alternative if no surgical capacity available is stereotactic radiotherapy)	Diagnostic work-up and/or resection of all other nodules of incidental finding including too: ► Solid nodule >500mm^3 and known VDT >600 days (alternative if no surgical capacity available is stereotactic radiotherapy)

GGO, ground-glass opacity; NSCLC, non-small cell lung cancer; VDT, volume doubling time.

The risk-benefit ratio of adjuvant chemotherapy should be thoroughly discussed with patients. The indication should be strongly considered in the presence of negative prognostic features (eg, lymphovascular infiltration, pathological lymph node invasion), while it should be withheld in frail, elderly patients with significant comorbidities. On the other hand, despite the risk of SARS-CoV-2 infection related to chemotherapy-induced immunosuppression, adjuvant chemotherapy should be proposed in fit and young patients (≤65 years), with resected T3/T4 or in case of pN2 disease.

Similarly, neoadjuvant chemotherapies should be given top priority, as reported by NHS clinical guide for the management non-coronavirus, in patients with cancer

Table 4 Medical oncology priorities: early stage disease

High priority	Medium priority	Low priority
Concomitant chemo-radiotherapy for SCLC limited disease stage I/II		
Neoadjuvant chemotherapy (enabling deferral of surgery by 3 months) in clinical stage II		
Medical follow-up between two cycles should be performed only if necessary and by telephone	Adjuvant chemotherapy in T2B-T3N0 or pN1 disease should be discussed with patients considering clinical features and prognosis Delivery of adjuvant chemotherapy in T3/4 or N2 disease for young (age ≤65/70 years old)* and fit patients	Adjuvant chemotherapy in stage T1A-T2BN0 with negative prognostic features (lymphovascular infiltration, …)
Laboratory check between two cycles should be performed only if necessary and at home if possible		Adjuvant chemotherapy for elderly (older than 65 years old) and patients with important comorbidities should be discussed and possibility omitted
G-CSF use if febrile neutropenia risk evaluated more than 10% to 15%		

*Defined elderly age according to local guidance.
G-CSF, granulocyte colony-stimulating factor; SCLC, small cell lung cancer.

Table 5 Medical oncology priorities: locally advanced disease

High priority	Medium priority	Low priority
Concomitant chemo-radiotherapy for SCLC limited disease stage III		
Concomitant or sequential chemo-radiotherapy for inoperable NSCLC Stage III		
Starting consolidation durvalumab (within 42 days)		
Neoadjuvant chemotherapy in clinical stage III	Medical follow-up between two cycles should be performed only if necessary and by telephone	
G-CSF use if febrile neutropenia risk evaluated more than 10% to 15%	Laboratory check during treatment should be performed only if necessary and at home if possible	

G-CSF, granulocyte colony-stimulating factor; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

requiring acute treatment. This approach applies potentially to all patients suitable for a surgical approach with curative intent, in particular, in young and fit patients without comorbidities. In adjuvant or neoadjuvant platinum-based chemotherapy, the use of granulocyte growth factors should be considered to avoid and minimise neutropenia and its related risk of hospitalisation, possibly beyond the usual recommendations.[27 28]

LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

The management of stage III of NSCLC is notably challenging during the COVID-19 pandemic, considering that the need to optimise and prioritise the appropriate combination, time and sequence of multiple treatment modalities, potentially lead to an increased risk of exposure within hospitals to SARS-CoV-2.[29]

Given the significant curative potential, the treatment for a patient with stage III NSCLC should receive high priority. These apply to neoadjuvant treatment in potentially resectable stage IIIA and to concomitant or sequential chemoradiation (CT/RT) in stage IIIA/IIIB/IIIC, both supported by the use of granulocyte colony-stimulating factor (G-CSF) as previously proposed. Similarly, as for patients with disease control after CT/RT treatment, the subsequent use of durvalumab as *consolidation* therapy should be guaranteed within 42 days after CT/RT completion, without any planned delay (table 5).

A durvalumab infusion every 4 weeks instead of the standard every 2 weeks should be considered, where allowed from National Regulatory Agency (high priority).

METASTATIC NON-SMALL CELL LUNG CANCER

The definition of a homogeneous prioritisation algorithm in the metastatic setting is complex. In the clinical landscape of active treatments known to improve quality of life and survival in a very aggressive malignancy, evidence-based treatment approaches should retain priority even during the pandemic. Nowadays, the COVID-19 outbreak represents an immediate threat to patients with NSCLC, but the possible disruption of cancer services might potentially outweigh the number of deaths from SARS-CoV-2 in the next years.[11]

According to the MCBS, the priority interventions in the advanced setting are scored 3, 4 or 5, in a descending scale for value, from 5 to 1.[12] For such, the magnitude of benefit and the expected treatment benefits should guide the clinical indications and support treatment decisions.

In order to limit cancer-related mortality, in patients with a new diagnosis of metastatic NSCLC, all standard options for first-line systemic therapy should be envisaged unaltered, including chemotherapy, immunotherapy, tyrosine kinase inhibitors and different combinations. This approach aims to improve prognosis, cancer-related symptoms and QoL and should be prioritised whenever possible. The same holds true for second-line treatments in patients with symptomatic, progressive disease, whereas delaying the treatment could compromise patient's survival (high priority) (table 6).

In both settings, when the chosen treatment for clinical or biological criteria is chemotherapy, the use of G-CSF has to be considered if risk of febrile neutropenia is above >10% (high priority). This is not anticipated to impact on the specific COVID-19 risk but could reduce significantly risk of neutropenic sepsis hence number of hospital admissions for neutropenic sepsis.

Based on pharmacokinetic modelling and exposure-response analyses, immune checkpoint inhibitors (ICIs) schedule should be modified/delayed to reduce clinical visit, using 4-weekly nivolumab 480 mg[30–34] or 6-weekly pembrolizumab 400 mg[35–37], instead of the standard 2-weekly or 3-weekly, when appropriate and where allowed from National Regulatory Agency (high priority).

For patients on ICI for more than 12/18 months, delaying the subsequent cycle, omitting some cycles or generally expanding intervals should be considered.[37–40] Discontinuation of ICIs after 2 years should be discussed, keeping in mind the lack of prospective evidence about optimal treatment duration in lung cancer.

The role of tyrosine kinase inhibitors (TKIs) in oncogene-driven NSCLC must continue unaltered, unless clinical situations require discontinuation (high

Table 6 Medical oncology priorities: metastatic lung disease

High priority	Medium priority	Low priority
First-line treatment including, chemo, chemo plus IO, IO alone or TKIs to improve prognosis, *cancer-related symptoms and QoL*	Start second-line and beyond-line chemotherapy or IO in asymptomatic patients, in absence of threatening disease (volume/location).	Discontinuation of ICIs after 2 years of treatment should be suggested
Start second-line chemotherapy or IO in symptomatic and progressive disease patients.	Consider when feasible, oral chemotherapy treatment instead of intravenous (etoposide, vinorelbine) to reduce hospital visits	For patients ongoing with ICIs having stopped due to toxicity, resuming might be delayed in absence of disease progression
Start second-line TKI in progressive disease patients.	Medical follow-up between two cycles should be performed only if necessary and by telephone	Postpone antiresorptive therapy (zoledronic acid, denosumab) that is urgently for hypercalcaemia
G-CSF use has to be considered if despite optimal dose modification, a risk of febrile neutropenia is >10%	Blood check during treatment should be performed only if necessary and at home if possible	
ICIs scheduled cycles may be modified/ delayed to reduce clinical visits (for instance, using 4 weekly or 6 weekly dosing instead of 2 weekly or 3 weekly for selected agents when appropriate (where allowed from National Regulatory Agency)	For patients ongoing with ICIs from more than 12/18 months, delaying the next cycle and omitting some scheduled cycles or generally enlarged intervals should be considered	

G-CSF, granulocyte colony-stimulating factor; ICI, immune checkpoint inhibitors; IO, immune-oncology; QoL, quality of life; TKI, tyrosine kinase inhibitors.

priority). A drug home delivery service should be instituted if possible for patients receiving oral TKIs to ensure similar drug access during the pandemic and unchanged care, while limiting access to hospital hence reducing the exposure to SARS-CoV-2

Home delivery service should be considered even in the case of oral chemotherapy treatments, which are preferred to the corresponding intravenous formulations, when available, such as etoposide or vinorelbine, when clinically needed to reduce hospital admissions (medium priority).

Extra caution is required by systemic treatments that are less likely to impact overall survival or quality of life. A full explanation and assessment of risk/benefit ratio should be discussed with the patient on a case-by-case basis.

In this emergency scenario, a temporary withdrawal of some interventions could be contemplated. Antiresorptive bone-protective therapy (zoledronic acid, denosumab), not deemed urgent for malignant hypercalcaemia, should be withheld unless deliverable in the community or at the patient's home (low priority).

SMALL CELL LUNG CANCER

SCLC treatment has always represented a challenge for the thoracic oncologist, considering the tumour aggressiveness, the rapid growth and early spread to distant metastases, sometimes associated with paraneoplastic syndromes.

As in the non-COVID-19 clinical setting, the treatment of SCLC should always be prioritised in patients suitable to receive first-line chemotherapy with or without ICIs for metastatic disease, or in patients with limited disease, treated concurrently with chest radiotherapy. G-CSF support is strongly indicated for patients who have a high or medium risk of febrile neutropenia (high priority) (tables 5 and 6).

Starting second-line therapy in a symptomatic and/or platinum-refractory patient should be extensively discussed with the patient, weighing risk/benefit ratio.

The administration of prophylactic cranial irradiation (PCI) should be potentially deferred in patients with limited stage, and replaced by MRI surveillance in patients with extensive disease SCLC.

RADIATION ONCOLOGY

The priority remains to guarantee that all curative treatments are unaffected by the COVID-19 pandemic. Recently the Royal College of Radiologist has issued guidelines on "Reduced fractionation in lung cancer patients treated with curative-intent radiotherapy during the COVID-19 pandemic".[41] They highlight the importance of discussing alternative dose-fractionation schedules of radiotherapy techniques. Timing and ability to implement changes to dose/fractionation schedules will vary depending on resources and technology available and current capabilities. The objective is to identify reduced-fractionation and curative-intent radiotherapy regimes in lung cancer, assess their evidence base and provide organs-at-risk dose constraints. The aim is first to reduce hospital visits and exposure to SARS-CoV-2 and to increase radiotherapy unit capacity for operable patients

Table 7 Radiation oncology priorities for lung disease

High priority	Medium priority	Low priority
Radiotherapy for inoperable stage II to III cancers, with contraindications for chemotherapy.	SABR - SBRT for stage I cancers	
Concomitant (preferred) chemo-radiotherapy for inoperable NSCLC Stage II/III. -	Adjuvant PORT for R1 resection, if indicated in NSCLC could be considered at the end of adjuvant chemotherapy or delayed up to 3 months from surgery	Adjuvant PORT N2 R0, if indicated in NSCLC should be discussed and if retained considered at the end of adjuvant chemotherapy or delayed up to 3 months from surgery
Concomitant (preferred) chemo-radiotherapy for SCLC limited disease	PCI in limited SCLC after chemotherapy	PCI in extensive stage SCLC after chemotherapy should be replaced by MRI active surveillance
Superior vein cave obstruction or significant haemoptysis, spinal cord compression or any threatening lesion amenable to radiation therapy		

NSCLC, non-small cell lung cancer; PCI, prophylactic cranial irradiation; PORT, post-operative radiation therapy; SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiotherapy; SCLC, small cell lung cancer.

with lung cancer who may not be able to have surgery during this pandemic.

Furthermore, ESTRO-ASTRO has issued some recommendations on how to adapt radiotherapy for lung cancer in the COVID-19 pandemic pointing out that all efforts should be made not to compromise the prognosis of lung cancer patients by departing from guideline-recommended radiotherapy practice.[42]

For instance, the adjuvant post-operative radiation therapy (PORT) for radically resected pN2 NSCLC should be discussed and eventually performed at the end of adjuvant chemotherapy or eventually delayed up to 3 months from surgery (low priority) (table 7). The same therapeutic approach with PORT, in R1 resection, could be considered at the of adjuvant therapy or delayed up to 3 months from surgery (medium priority).

For inoperable or locally advanced stage II to III lung cancers, the radiation, alone or with concurrent or sequential chemotherapy, should be delivered given the curative potential (high priority). At the same time, palliative radiotherapy should not be denied or delayed in life-threatening or highly symptomatic clinical conditions, as superior vena cava obstruction, spinal cord compression, significant dyspnoea, bleeding or bone pain (high priority). Palliative RT with a single fraction or two fractions could be considered as an alternative to longer fractionation whenever possible.

The curative treatment for stage I lung cancer should be given with stereotactic body radiotherapy. In very early stage I patients, this treatment may be delayed in order to protect the patient by limiting hospital access during the pandemic peak (medium priority). A single fraction of 30 to 34 Gy should be considered depending on tumour location.

As far as SCLC is concerned, MRI surveillance should be preferred to PCI for extensive-stage SCLC in order to reduce the number of visits (low priority); alternatively, PCI in limited-stage SCLC could be considered after chemotherapy (medium priority).

COVID-19 AND ITS IMPACT ON LUNG CANCER RESEARCH

Strict measures to limit the virus spread have affected clinical cancer research centres that decreased their activity due to quarantine, working in shifts and lack of supplies. In some of these centres it was necessary to make decisions of interrupting or even permanently stopping some trials in order to preserve the accuracy of endpoint evaluation and the protocol adherence. While clinical and translational research is crucial for providing the best care for cancer patients, many centres faced the need to modify programmes and adapt them to the new situation. Difficulties in trial conduction and monitoring may lead to specific and potentially critical protocol deviations. Despite this rapid evolution of the COVID-19, there is a strong need to respect several important aspects. First, all patients on trials should be ascertained a safe continuation of protocol treatments. Second, all efforts should be made to protect patients by minimising unnecessary visits to cancer unit. Patients must consent to pursue their experimental trial care in the evolving COVID-19 situation after having been adequately informed about risk/benefit ratios.

Nonetheless, the clinical trial investigating specific treatment for COVID-19 have been prioritised, following the absolute clinical need.[43 44]

In lung cancer research, enrolling or treating patients in trials with target therapy or ICIs should be prioritised, while reducing, if feasible, visits and planned hospital admission according to sponsors and clinical investigators.

To withdraw optional trial procedure and to allow flexibility in visits, imaging assessments and laboratory checks should be considered via protocol amendments as necessary. Trials with a placebo arm should be suspended until

the pandemic resolves, as exposing patients to the risk of SARS-CoV-2 in this context would be difficult to justify

To properly manage clinical trials during the COVID-19 pandemic, the leading regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued guidelines and recommendations for a safe delivery of the study medications and a structural information on changes and protocol deviations.[45 46]

CONCLUSION

The COVID-19 has put a strain on the global healthcare system leading to an unprecedented modification of patient care and access to health services. During this pandemic, maintaining cancer care has represented a challenge that has required careful weighing of the COVID-19 risk and the optimal oncological standards.[47]

The oncology community has been forced to adapt cancer care and identify new strategies and priorities to ensure the highest possible therapeutic standards for our patients. Following the WHO indications, the development of a framework to provide clear guidance on healthcare priorities, to support and enable decision-making when resources need to be rationed and cautiously allocated. Any possible modification of a treatment schedule should entail a multidimensional assessment adapted to local resources, comprising clinical and tumour characteristics, therapeutic objective and the potential risks associated with COVID-19 infection.

The ESMO clinical recommendations for lung cancer management are, in this context, a guide to ensure and maintain high-quality standards for our patients.

Unfortunately, to date, robust data are lacking to guide adjustments to standard-of-care in patients with lung cancer. Individualised treatment strategies and close follow-up are needed to reduce the gaps of COVID-19 in our patients and to improve evidence-based approach and policies during this pandemic.

Useful and updated information can be found at https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/lung-cancer-in-the-covid-19-era

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Contributors AP and SP developed the first outline, based on the ESMO recommendations already published online and developed with AA, CvG and HB. AP and SP coordinated the authors' contributions, engaged for competencies and expertise in the management of lung cancer. All the authors were involved in writing and, when the first draft had been developed, all the authors refined the contents with feedbacks and comments, incorporated by AP, AA and SP. All the authors approved the final draft before the submission. While the authors are affiliated to different institutions for cancer research and care, the perspectives expressed in the present paper should not be intended to mirror the societal and institutional positions.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests AP: honoraria for consulting, advisory role or lectures from AstraZeneca, Agilent/Dako, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme and Roche Genentech. AA: honoraria for consulting, advisory role from AstraZeneca, Bristol-Myers Squibb, Merck Sharpe & Dohme, Takeda, Pfizer, Roche Genentech and Boehringer Ingelheim. CvG: honoraria for consulting, advisory role or lectures from AstraZeneca, Boehringer Ingelheim, GSK, Mundipharma, Novartis, Pfizer, PneumRx et Pulmonx. FB: honoraria for consulting, advisory role or lectures from AstraZeneca, Abbvie, Bayer, Roche Genentech, Pfizer, Cell Medica, Celgene, Takeda. DP: honoraria for consulting, advisory role or lectures from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche Genentech, Samsung Honoraria: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche. EF: advisory role or speaker's bureau from AbbVie, AstraZeneca, Blueprint medicines, Boehringer Ingelheim, Bristol-Myers Squibb, GSK, Eli Lilly, Guardant Health, Janssen, Medscape, Merck KGaA, Merck Sharp & Dohme, Novartis, Pfizer, prIME Oncology, Roche Genentech, Samsung, Springer, Takeda, Touchime. Board: Grifols, independent member Research funding: Fundación Merck Salud, Grant for Oncology Innovation EMD Serono. RD: honoraria for consulting, advisory role or lectures from from AstraZeneca, Roche, Pfizer, Novartis, Seattle Genetics, Foundation Medicine, Bristol-Myers Squibb, Takeda. FdM: honoraria for consulting, advisory role or lectures from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Merck Sharp & Dohme, Novartis, Roche Genentech, Takeda and Pfizer. MR: honoraria for consulting, advisory role or lecture from Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Merck, MSD, Novartis, Pfizer, Roche, Samsung. Support for clinical research from BMS. HB: honoraria for consulting, advisory role or lecture for AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Roche Genentech. SP: received education grants, provided consultation, attended advisory boards, or provided lectures for Abbvie, Amgen, AstraZeneca, Bayer, Biocartis, Bioinvent, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F Hoffmann-La Roche, Foundation Medicine, Illumina, Janssen, Merck Sharp & Dohme, Merck Serono, Merrimack, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics, Takeda and Vaccibody, from whom she has received honoraria (all fees to institution).

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

Data availability statement No data are available.

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